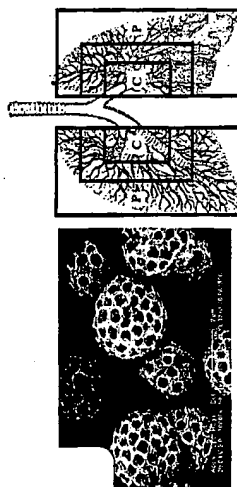


Advanced DRUG DELIVERY Reviews

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AEROSOL DELIVERY
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Novel alternative methods for the delivery of drugs for the treatment of asthma

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Abstract

Successful delivery of dry powder aerosols to the lung requires careful consideration of the powder production process, formulation and inhaler device. Newer production methods are emerging to prepare powders with desirable characteristics for inhalational administration. The conventional formulation approach of adding coarse lactose carriers to the drug to form binary powder systems to enhance powder flow and dispersion properties has been expanded to using finer carrier particles and hydrophobic materials, as well as ternary systems. Particle morphology and surface properties have also been explored to enhance powder performance. For the inhaler device, the new generation inhalers are designed to reduce or completely decouple the influence of air flow on the aerosol generation. Each of these determinants for powder aerosol delivery is reviewed with a strong focus on the patent literature that contains enormous information about the latest development in this field.

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Keywords: Dry powder aerosol formulation; Powder production process; Spray drying; Solvent precipitation; Milling; Powder properties; Carrier blend; Dry powder inhaler

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1. Introduction

Manufacturing of dry powder inhaler products for inhalational drug administration requires powders with desirable characteristics. For decades, powders for inhalation have been produced by crystallization followed by milling to micronize the particles to the required size suitable for aerosol formulation and delivery to the lung. This production approach has a major disadvantage of poor control over the particle shape and size, and size distribution. Milling also tends to produce a partially amorphous state of matter, leading to potential instability problems. An additional problem is that malleable materials such as inhaled steroid drugs (e.g., triamcinolone acetonide) are difficult to mill [1]. Despite these limitations, crystallization and milling are established techniques and have been widely used in the past for inhalation products [2–4].

Micronized powders are cohesive with poor flowability, making both filling and emptying of powder into and out of the inhaler or capsule difficult and irreproducible. Conventionally the problem was solved by particle size enlargement, either via forming agglomerates or using large carriers. In either case, the drug has to be recovered by dispersion as fine particles during aerosol generation for inhalation. Typically the micronized drug is blended with coarse carrier lactose of 30–80 µm or larger to form an 'ordered mix' [5–7]. In the second approach, the drug itself is formulated as soft pellets, agglomerates

or granules. Pelletization is usually achieved by (a) moistening the medicament powder by a small amount of liquid followed by extruding the moistened powder through an orifice and drying, or (b) agglomeration in a controlled environment (e.g., at elevated vapor pressure of a liquid) inside a fluidized bed. For both methods, depending on the hygroscopicity of the drugs, the liquid or vapor used can be water or organic solvent [8,9]. The level of liquid or adsorbed vapor is finely adjusted to cause weak particle cohesion so that loose bridges between particles would form on evaporation of the liquid. Water is preferred as residual organic solvent can be a concern. The moisture content of the pellets is critical according to the physical properties of the particulate material, e.g., 8–11% for sodium cromoglycate [8]. Pelletization can be both difficult and expensive as it involves extra manufacturing steps.

As a result of the growing interest in aerosol drug delivery to the lung for local and systemic effects, together with the new drug candidates (small and macromolecules, e.g., heparin [10], Cys-LT receptor antagonists, synthase inhibitors (e.g., Zafirlukast) [11] and antisense oligonucleotide [12]) for asthma treatment, the efficiency of delivery has to be optimized. This is being achieved by improving the powder production process, aerosol device performance and powder properties. Topics on these areas have been recently reviewed [13,14]. The present article has a particular emphasis on the patent

literature about the most recent development in this field.

2. Emerging powder production methods

While the conventional methods of powder production for inhalation products may have been sufficient in the past, they are not suitable to produce powders with the required flow and dispersion characteristics to meet the need of enhanced powder performance. Various methods that have been explored or are in their advanced stage of development will be discussed here.

2.1. Spray drying and related droplet evaporation methods

2.1.1. Spray drying

Spray drying was explored in the 1980s as an alternative means of making fine particles with desirable flow and dispersion characteristics without the need of using coarse carriers or forming soft pellets. Anti-asthmatic drugs including salbutamol sulfate, terbutaline sulfate, isoprenaline sulfate and sodium cromoglycate were investigated [15–17]. However, it was not until the early 1990s when the potential of the pulmonary route for therapeutic proteins delivery has been recognized, then an enormous effort was focused on spray drying of pharmaceuticals.

In spray drying, a drug solution is atomized to fine droplets which are evaporated in a warm air current to form dry particles [18] (Fig. 1). Although the drying air temperature can be relatively high (e.g., >100 °C), the actual temperature of the evaporating droplets is significantly lower due to cooling by the latent heat of vaporization. Thus, thermal degradation of the active ingredient is not so much a concern as it first appears.

In addition to drug production, spray drying has been used to produce carrier particles, e.g., spherical lactose carrier particles for budesonide formulation has been prepared by this method [25].

Spray drying is not limited to aqueous solutions. Spray drying of ethanolic solutions containing sal-

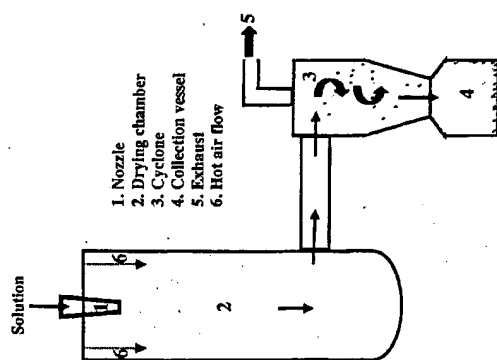


Fig. 1. Schematic diagram of the spray drying process.

reported [19]. Pure beclomethasone dipropionate (BPD) particles and BPD-hydroxypropylcellulose particles for controlled release in the lung have been produced by the same method [20]. Non-aqueous systems have also been used to prepare porous particles suitable for aerosol delivery [21–24].

The properties of the spray dried powders are controlled by both the process and formulation parameters. Earlier studies have looked into the effects of the active ingredient, atomizing nozzle type, powder collection technique and droplet drying time [16,18,26]. The liquid feed can be atomized by rotary nozzle, two-fluid nozzles, or ultrasonic nozzles, depending on the droplet size required. Powder collection is usually achieved by using a cyclone but a filter bag can also be used. The latter is not preferred since particulate of the filler material may contaminate the powder. The driving force for drying is controlled by the water content and the difference

in the inlet and outlet temperatures of the drying air. Drying time of the droplets depends on the residence time of the droplets in the spray drier which, in turn, is determined by the spray drier dimension and the drying air flow rate. It is important to note that these parameters are closely interrelated. Changing a process parameter will therefore lead to a change in the others. For example, while reducing the air flow will lengthen the time for the droplets to evaporate, the drying efficiency will be reduced simultaneously because less air is available to evaporate the droplets. A lower drying air flow will also decrease the collection efficiency of the cyclone. However, higher air flow will evaporate the droplets more rapidly, resulting in a less crystalline product due to insufficient time allowed for crystallization. Thus, the usefulness of spray drying to prepare stable fine particles is hampered. This becomes obvious since spray dried powders tend to be amorphous as found for sodium cromoglycate and salbutamol sulfate [15,17]. This is a significant drawback as amorphous materials are hygroscopic, more cohesive and difficult to flow and disperse. To facilitate crystallization, the drying time can be prolonged by inserting a secondary drying apparatus between the primary drying chamber and the cyclone as described in a recent patent [27]. Another limitation of spray drying is its unsuitability for substances sensitive to mechanical shear of atomization [26]. Drugs that are

2.1.3. Controlled evaporation of droplets

Like spray drying, this is a single-step continuous process involving atomizing the drug solution into a carrier gas for drying [31,32]. Unlike spray drying, this method provides better control over the temperature history and residence time of droplets. In the actual setup, the solution is atomized using an ultrasonic nebulizer. The droplets suspended in a carrier gas are then fed into a tubular flow reactor housed in a constant temperature oven for evaporation. Since the feed rate and temperature are adjustable, the temperature history and residence time of the droplets can be controlled. The method has the potential to control the particle morphology and polymorphic form and has been used to produce beclomethasone dipropionate particles.

2.1.4. Evaporation of low-boiling-point solutions

This involves simply dissolving the active ingredient in a low-boiling-point organic solvent followed by atomizing the solution and evaporating the resulting droplets to produce the dry particles [33]. The

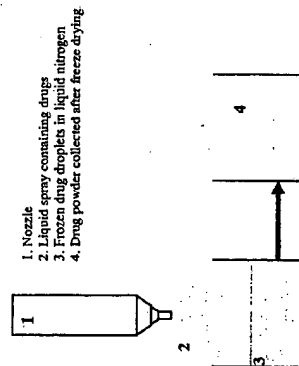


Fig. 2. Schematic diagram of the spray freeze drying process.

concept of this approach is similar to both spray drying and rapid expansion of supercritical fluid.

2.2. Solvent precipitation

2.2.1. Sono-crystallization

Inhalable particles can potentially be obtained by rapid precipitation from aqueous solutions using anti-solvents. However, due to dispersion in the nucleation rate and crystal growth, it is difficult to reproducibly generate particle size in the micron range for aerosol delivery. Recently, ultrasonic radiation has been applied to control the precipitation process [34]. The setup can simply comprise an ultrasound probe in a mechanically stirred reaction tank where the anti-solvent is mixed with the drug solution to precipitate the fine drug particles. The ultrasound frequency is crucial and 20–25 kHz (or higher) was reported suitable for setups similar to the one shown in Fig. 3. Examples of anti-asthmatic drugs prepared using this sono-crystallization technique include fluticasone propionate and salmeterol xinafoate [34]. This method should be applicable to prepare other inhalable compounds such as salbutamol sulfate, beclomethasone dipropionate, budesonide, and formoterol fumarate.

2.2.2. Microprecipitation by opposing liquid jets
In this method, precipitation occurs in a region of extreme turbulence and intense mixing created by a jet of drug solution opposing a jet of anti-solvent coming through two opposing nozzles mounted in a small chamber [1]. As two liquid jets mix, the anti-solvent will cause the drug to precipitate as fine particles. The crucial process parameters include the speed of the liquid jets and concentration of the drug solution. A high jet stream speed or a high drug concentration was found to give finer particles but higher residual solvent level and vice versa. The volume ratio of drug solution to anti-solvent is also expected to affect the precipitation process.

2.2.3. Supercritical fluid (SCF) technology

The SCF technology has successfully been used to prepare antiasthmatic compounds [35,36]. Details of this novel technology can be found in the article written by Peter York and colleagues in this volume.

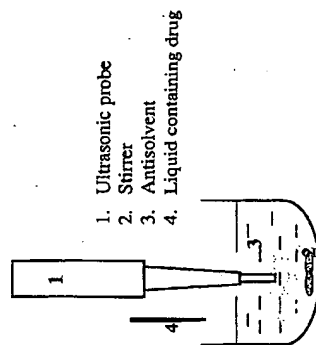


Fig. 3. Schematic diagram of the sono-crystallization process.

2.3. Specialized milling

Dry milling tends to produce partially amorphous materials with surface charge causing particle agglomeration. These problems can be dealt with by specialized milling methods.

2.3.1. Fluid energy milling at elevated humidity

In order to reduce the amorphous content in the material produced by milling, the latter can be carried out at elevated humidity to facilitate *in situ* crystallization. The milled products have been reported to be predominantly crystalline with particle size distribution similar to those produced by the conventional milling process. The setup involves a control of the relative humidity (e.g., 30–70%) of the milling chamber by humidifying the feed gas (e.g., by superheated steam to minimize condensation) used for milling the powder [37].

2.3.2. Wet milling nanotechnology

Nanocrystal® (Elan Pharmaceutical Technologies, King of Prussia, PA, USA) technology is an aqueous-based milling process to reduce particle size to below 400 nm. A conventional ball mill can be used for the process, and the materials selected for the grinding media (e.g., glass, zirconium oxide) were reported to be not crucial. However, the size of the grinding media are preferably 1 mm or less in order to be

effective in attrition and imparting less wear to the mill [38]. Since the particles are produced in water, any amorphous regions in the particles would undergo recrystallization. Thus the wet-milled powder is anticipated to be crystalline and more stable to moisture than powders produced by dry milling. Budesonide was milled to a particle size of 166 nm in an aqueous dispersion, which was then spray dried to produce powder with a mean particle size of 1.35 µm [39]. A surface modifier (e.g., polyvinyl pyrrolidone (PVP), lecithin, cellulose derivatives) is added during or after milling to prevent agglomeration of the nanoparticles. Although these stabilizers can be of GRAS materials, long-term inhalation can be a concern unless proven safe. Another major drawback of wet milling is that, depending on the type of mill and the drug, a lengthy processing time may be required (up to 5 days or longer).

3. Strategies for dry powder aerosol formulations

3.1. Use of crystalline instead of amorphous materials

A common problem encountered in making stable dry powder inhalation products is the amorphous nature of micronized drugs (and even the excipients) which is a result of the grinding, milling or spray drying process used to produce the required finely divided particles. Amorphous materials are physically unstable and in high humidity will recrystallize uncontrollably, forming solid bridges between particles. Consequently the powder dispersibility will decline during storage. However, if these amorphous materials can be rendered crystalline in a post-production treatment, the powder stability will be increased. This has been achieved by conditioning the amorphous particles through exposure to a controlled environment [e.g., 35–85% relative humidity (RH) or organic solvent vapor] to induce crystallization and has been applied to anti-asthmatic drugs such as salbutamol sulfate, ipratropium bromide, formoterol fumarate dihydrate, terbutaline sulfate and budesonide [40]. The process can be carried out in a closed container (e.g., a column or a flask) or in a

fluidized bed dryer at controlled temperature and humidity, and has been employed to transform the spray dried amorphous spherical lactose carrier to the crystalline alpha monohydrate form used for sodium cromoglycate and budesonide [25]. In one particular case, it was found that conditioning albuterol sulfate–lactose formulation at high humidity alone was not sufficient, and fine (<3 µm) albuterol sulfate particles have to be removed in order to maintain the formulation stability during storage. The instability was believed to be due to the smaller particles which being more energetic, caused fusion among themselves and with the larger particles [41].

3.2. Use of suitable excipients in blend formulations

Blends have been prepared by mixing excipient(s) with the active drug to form a binary or ternary blend. There is a number of strategies using excipients to improve the powder properties for the purpose of:

- (I) Promoting release of the active drug from carrier particles.
- (II) Improving powder flowability.
- (III) Improving moisture resistance and storage stability.
- (IV) Combination of I, II and III.

3.2.1. Fine particle excipient

Fine lactose particles (~5 µm) have been used to enhance the dispersibility of salbutamol sulfate and nedocromil sodium [42] (Table 1). The fine lactose powder was mixed with the coarse lactose carrier before adding in the salbutamol sulfate or mixed with the pre-blended coarse lactose carrier and salbutamol sulfate to form multiplets. For nedocromil sodium, the drug was directly blended with the fine lactose particles without the coarse carrier. It was suggested that the fine lactose particles disrupt the strong cohesion of nedocromil sodium. In both cases, the drug particles will be easier to detach from the powder formulation due to reduced cohesion force. However, the deposition of fine carriers in the lung may raise clinical and regulatory concerns.

Table 1
Effect of fine particles on aerosol performance [42]

Formulation	% Fine particle fraction (with reference to emitted dose)
Salbutamol sulfate + coarse lactose	19.2
Salbutamol sulfate + (coarse lactose + finer lactose)	36.4
Finer lactose + (salbutamol sulfate + coarse lactose)	38.0
Nedocromil sodium + coarse lactose (40:60)	19.3
Nedocromil sodium + finer lactose (40:60)	50.4

3.2.2. Ternary additive with lubricant or anti-adherent properties

In this process, the additive is first mixed with the carrier to form 'composite' excipient particles [43], followed by adding in the active drug. This procedure of mixing the ingredient is considered important as it allows the additive material to first occupy the high energy binding site on the carrier, thus making the weakly bound active particles easier to release from the carrier during dispersion. The method has been attempted on anti-asthmatic drugs including beclomethasone dipropionate, budesonide, and salbutamol base. Magnesium stearate in particular, a hydrophobic excipient, has been widely employed for this purpose in recent patents [44,45]. Formulation containing salbutamol sulfate (2.5 wt.%), mixed with lactose monohydrate (97 wt.%) as carrier and magnesium stearate, (0.5 wt.%) as additive has been shown to provide moisture resistance and storage stability at 75% RH and 40 °C. The same applies to another preparation containing the long acting bronchodilator, formoterol fumarate dihydrate (0.3 wt.%) formulated as an admixture with lactose carrier (99.2%) and magnesium stearate (0.5 wt.%) [46,47]. Improved aerosol performance

for similar formulations containing the same active drugs have also been reported [48]. It is obvious in these examples that only a small amount (<0.5 wt.%) of the ternary additive is usually required to impart an improvement to the powder formulation [49,50]. This is expected as the surface-to-volume ratio of the coarse carrier particles is relatively low and only the surface of the carrier needs to be covered to have the surface properties modified. There is no further advantage of using a higher concentration of Mg stearate. In fact, it could actually reduce the fine particle fraction of drug in the aerosol [49] (Table 2). A single-dose tolerance study in healthy subjects and a 3-month toxicity study in asthmatic patients showed no accumulation of magnesium in the bronchial or alveolar cells [49]. Besides Mg stearate, other hydrophobic compounds such as leucine, lecithin, stearic acid and their derivatives were also reported to be suitable additives [43,51–54].

It should be noted that the additive material, instead of being an excipient, can itself be a second active drug. This approach has been applied to a fluticasone and formoterol combined formulation [55]. In this case, the non-polar fluticasone was first

Table 2
Effect of magnesium stearate on aerosol performance of budesonide dipropionate and salbutamol sulfate [49]

Formulation	Magnesium stearate (wt.%)	Fine particle dose (200 µg/dose)
Budesonide dipropionate	0	7.3
	0.25	25.0
	0.50	16.7
Salbutamol sulfate	0	33.6
	0.25	41.6
	0.50	39.9

blended with lactose carrier to saturate the high energy sites on the polar lactose surface. The polar formoterol particles were then added which however were prevented from coming into direct contact with the lactose surface (or at least those pre-occupied higher energy sites). This resulted in a polar/non-polar/polar composite agglomerate which was less susceptible to the influence of humidity due to the non-polar partition layer.

In a special application, the fine excipient material was used to coat the active drug so as to modify its surface electrical properties [56]. Powders of active ingredients and/or excipients suitable for electrostatic charging have been prepared by this method. Inhalable aerosols can then be generated using a specialized inhaler capable of charging up the powder for dispersion [57].

3.3. Use of particles with designed features

Since the aerodynamic diameter depends on the particle density, whereas the inter-particle cohesion force and hygroscopicity depends on the surface morphology and chemical nature, these parameters can be modified to enhance the aerosol performance and moisture stability of the powder.

3.3.1. Co-spray drying with a suitable excipient

The choice of excipients is demonstrably critical for powder dispersion. Sodium chloride increased the dispersibility of spray dried protein rhDNase with increase of powder crystallinity. NaCl crystals were observed on the surface of the protein particles [58]. The dispersibility enhancement was attributed to decreased cohesion as a result of changes in surface energy and morphology of the crystalline particles. It has been reported that the effect of moisture on powder dispersion can be instantaneous [59]. A possible way to reduce the hygroscopic effect is to use hydrophobic excipients. For example, spray dried particles of L-isoleucine, a hydrophobic amino acid, were shown to have superior physical stability at 40 °C/75% RH for 6 months [60]. D,L-leucine and therapeutic peptides to improve the aerosol performance by enriching the particle surface with these hydrophobic amino acids [61]. More recently, sodium cromoglycate has been co-spray dried with

hydrophobic amino acids, in particular leucine, to increase the powder dispersibility [62]. Surface analysis by X-ray photoelectron spectroscopy showed an enrichment of leucine on the surface of the cromoglycate particles, indicating that the improvement on dispersion is due to formation of a more hydrophobic particle surface.

3.3.2. Wrinkled particles

Surface morphology has been explored to improve dispersibility. Non-porous solid albumin particles with wrinkled surface were shown to give a significantly higher fine particle fraction (i.e. mass fraction of particles less than 5 microns in the aerosol as referenced against the total recovered dose) (FPF) than the non-wrinkled spherical particles (Fig. 4a) [63]. This was attributed to a reduced cohesion as a result of less close contact between particles. A distinct advantage of these wrinkled particles is that their dispersion performance is less dependent on the inhaler device and air flow (Fig. 4b).

3.3.3. Large porous particles

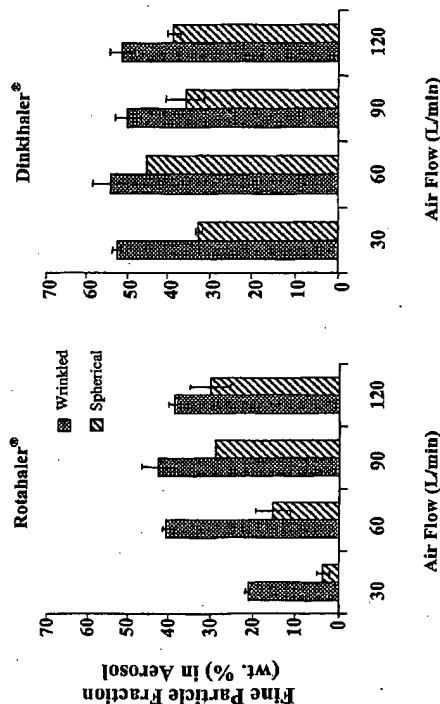
Large, porous particles (AIR™, mean diameter 5–20 µm, specific surface area ~50–100 m²/g, Alkermes, MA, USA) have been prepared to improve fine particle fraction due to the low density (<0.4 g/ml) giving rise to a small aerodynamic diameter, as observed in particles containing insulin (20 wt.%) and poly(lactic acid-co-glycolic acid) (PLGA) (80 wt.%) [64]. The superior aerosol performance of porous particles was also observed in anti-IgE powders [65] and was attributed to decreased cohesiveness of these particles.

3.3.4. Pulmospheres

Pulmospheres™ (Fig. 5, Nektar Therapeutics, San Carlos, CA, USA) are also porous particles with excellent dispersibility, but smaller in size (3–5 µm). These particles have been used to deliver immunoglobulin to the respiratory tract [66]. In addition, gentamycin, budesonide and albuterol particles have also been prepared by this technology [67]. The superior aerosol performance of budesonide Pulmosphere™ is summarized in Table 3 [68].



(a)



(b)

Fig. 4. (a) Wrinkled particles of bovine serum albumin (BSA); (b) superior fine particle fraction from wrinkled BSA particles as compared with spherical BSA particles. (Reprinted with permission, Kluwer Academic-Plenum Publishers, New York).

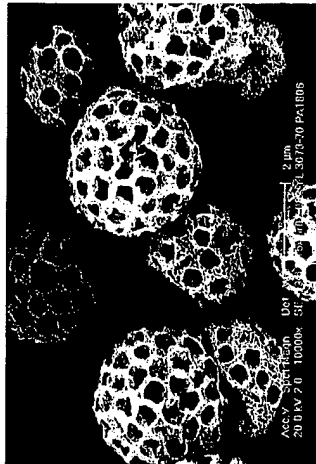


Fig. 5. Pulmophere™. (Courtesy of Dr. Jeff Weers, Nektar Therapeutics Inc., San Carlos, CA, USA).

Table 3
Aerosol performance of buderontide Pulmophers™ (Information taken from Ref. [66]. Copyright 2002. Reprinted with permission, Davis Horwood, North Carolina, USA)

Powder MMD (μm)	Powder MMAD (μm)	Fine particle fraction (% <5.8 μm)
2.1±1.7	2.9±1.7	84
2.5±1.7	3.2±1.7	88
3.5±1.6	3.4±1.5	99
4.9±1.6	3.9±1.5	92

4. Next generation dry powder inhalers

The existing marketed dry powder inhalers rely heavily on the patient's inspiratory effort to generate sufficient air flow for powder dispersion. New generation inhalers reduce or even completely decouple the influence of air flow on the aerosol generation. Three representative examples will be discussed briefly here.

4.1. FlowCaps® (Hovione)

FlowCaps® (Fig. 6) is a simple, breath actuated device designed to deliver an aerosol dose with minimum inspiratory effort. It operates at 30 l/min but works even at 20 l/min [69]. The dispersion

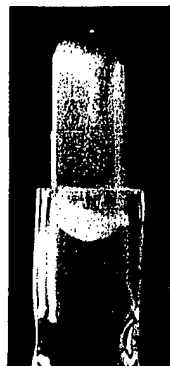


Fig. 6. Photograph showing the dispersion of powders within the capsule in a Hovione SA FlowCap® dry powder inhaler. (Courtesy of Hovione Production Farmaceuticos SA, Portugal).

mechanism involves slitting the ends of the capsule, followed by inhalation which creates a pressure difference across the capsule, forming turbulence flow like a cyclone inside the capsule to empty and disperse the powder out. The device can hold multiple capsules.

4.2. Spiros® S2 System (Elan Pharmaceuticals)

This inhaler is also designed to achieve efficient aerosol performance at low inspiratory flow (15–30 l/min) by the patient. The powder is dispersed by air entrained into the dose chamber containing a number of swirling beads to generate fluctuating shear zones for breaking up the powder agglomerates [70]. This

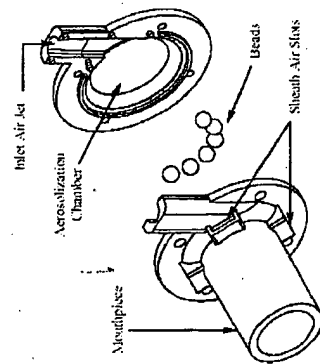


Fig. 7. Spino® S2 system. Copyright 2002. Reprinted with permission. Davis Horwood International, North Carolina, USA.

device is quite small and thus highly pocketable (Fig. 7).

4.3. Nektar Pulmonary Inhaler (Nektar Therapeutics)

The Nektar Pulmonary Inhaler (<http://www.nektar.com/content/inhalers>) is powered by a stored bolus of compressed air and is designed to generate aerosol completely independent of the patient's inspiratory air flow. Instead of leaving the inhaler directly and enter into the mouth, the powder is dispersed into a holding chamber from which the patient inhale the dose. A unit dose of powder is contained in individual aluminum blister to provide superior protection from moisture. The only drawback is the inhaler size which is relatively large to carry compared with other inhalers.

5. Conclusions

The key aspects on powder production process, powder formulation and inhaler device required for successful delivery of dry powder aerosols to the lung for the treatment of asthma have been reviewed with a focus on the emerging technologies which can

be used to overcome the limitations of the current methods.

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